

## **REMARKS**

Claims 1-6 and 10-16 are pending.

### **Claim Rejections -- 35 U.S.C. § 112, second paragraph**

Applicants respectfully traverse the rejections of claims 1-3 as allegedly being indefinite. The Office Action asserts that the subject matter of claims 1-3 is unclear. Applicants disagree. A person skilled in the art would readily understand that claim 1 is drawn to fexofenadine HCl characterized by the power X-ray diffraction (PXRD) peaks recited in claim 1. Claim 2 depends on claim 1. The person would understand that claim 2 is drawn to the fexofenadine HCl characterized by the PXRD pattern substantially as depicted in Figure 6, which contains the PXRD peaks recited in claim 1. Claim 3 is directed to fexofenadine HCl Form IX. According to page 12, lines 11-16, of the instant specification, fexofenadine HCl Form IX is a solvate of cyclohexane or MTBE, characterized by the same PXRD pattern as depicted in Figure 6 with the same PXRD peaks as recited in claim 1. Therefore, the person skilled in the art would know that claims 1-3 are directed to a cyclohexane solvate or MTBE solvate of fexofenadine HCl characterized by the PXRD peaks at about 4.7, 9.3, 17.4, 18.2, 19.4, 19.6, 21.6 and  $24.0 \pm 0.2$  degrees two theta, or characterized by the PXRD pattern substantially as depicted in Figure 6. Since the metes and bounds of claims 1-3 are clear to the person skilled in the art, withdrawal of the indefiniteness rejections of claims 1-3 is requested.

### **Claim Rejection -- 35 U.S.C. § 112, first paragraph**

Applicants respectfully traverse the rejection of claim 15 under 35 U.S.C. § 112, first paragraph allegedly for nonenablement. Claim 15 is directed toward a unit dosage of a pharmaceutical composition comprising solid fexofenadine HCl Form IX-cyclohexane solvate or solid fexofenadine HCl Form IX-MTBE solvate, wherein the unit dosage contains about 30 to about 180 mg of fexofenadine HCl. The Office Action asserts that the processes disclosed in pages 22-24 of the specification used to make the formulation will clearly transform any crystalline form. Applicants disagree. There is no evidence that the crystalline fexofenadine hydrochloride Form IX-MTBE solvate or Form

IX-cyclohexane solvate will change when subjected to the processes disclosed in pages 22-24. Guided by the disclosures of the specification supplemented with the knowledge in the art, a person skilled in the art will be able to prepare the unit dosage of claim 15 without undue experimentation. Thus, claim 15 is enabled.

#### **Claim Rejections -- 35 U.S.C. § 102(b)**

I. Applicants respectfully traverse the rejections of claims 1 and 2 as allegedly anticipated by Ortyl '872 (US 5,738,872). The Office Action alleges that claims 1 and 2 are anticipated by Ortyl '872 by asserting that the PXRD peaks at 9.3, 17.4, 18.2, 19.4, 19.6, 21.6 and  $24.0 \pm 0.2$  degrees two theta recited in claim 1 correspond to the PXRD peaks of 11.41, 5.23, 5.14, 4.72, 4.40, 4.18 and 3.85 Angstroms D-space of the crystalline fexofenadine HCl disclosed in Table 19 of Ortyl '872. Applicants disagree.

Using Bragg's law,  $n\lambda = 2d\sin\theta$ , with  $n = 1$  and  $\lambda = 1.5418$  Angstrom (see page 26, line 13, of the instant specification), applicants have calculated that the PXRD peaks of 11.41, 5.23, 5.14, 4.72, 4.40, 4.18 and 3.85 Angstroms D-space of the crystalline fexofenadine HCl disclosed in Table 19 of Ortyl '872 correspond to 7.8, 17.0, 17.3, 18.8, 20.2, 21.3 and 23.1 degrees two theta. At least the PXRD peaks at 7.8, 17.0, 18.8, 20.2, 21. and 23.1 degrees two theta of the crystalline fexofenadine HCl disclosed in Table 19 of Ortyl '872 do not match any of the PXRD peaks recited in claim 1.

The crystalline fexofenadine HCl disclosed in Table 19 of Ortyl '872 is different from the fexofenadine HCl crystalline forms of claims 1 and 2 because the crystalline fexofenadine HCl disclosed in Table 19 of Ortyl '872 lacks at least the following PXRD peaks: 4.7, 9.3, 19.4, 19.6 and 21.6 degrees  $2\theta$  recited in claim 1 and substantially as depicted in Fig. 6 recited in claim 2. The Office Action errs in stating that, "by PXRD alone, the same peaks are found i.e. identical pattern," when comparing the crystalline fexofenadine HCl according to claims 1-2 and the crystalline fexofenadine HCl disclosed in Table 19 of Ortyl '872. Applicants contend that Ortyl '872 fails to anticipate claims 1 and 2 because Ortyl '872 does not disclose crystalline fexofenadine HCl having all the characteristic PXRD peaks recited in claim 1 and 2. Withdrawal of the anticipatory rejections of claims 1 and 2 over Ortyl '872 is requested.

II. Applicants respectfully traverse the rejection of claim 16 as allegedly anticipated by Carr (US 4,254,129). Claim 16 is directed to a method of inhibiting binding between an H<sub>1</sub> receptor and histamine in a mammal comprising administering a pharmaceutical composition comprising solid fexofenadine HCl Form IX-cyclohexane solvate or solid fexofenadine HCl Form IX-MTBE solvate.

The Office Action asserts that the small genus of fexofenadine and hydrochloride salts found in Examples 2 and 3 of Carr anticipates claim 16. Applicants disagree. Examples 2 and 3 of Carr merely disclose fexofenadine hydrochloride recrystallized from butanone and methanol-butanone (Example 2) or from methanol-butanone (Example 3). Carr does not disclose the methyl t-butyl ether or cyclohexane solvate of fexofenadine hydrochloride. As a result, Carr does not disclose the pharmaceutical composition administered in the method of claim 16 to inhibit the binding between an H<sub>1</sub> receptor and histamine in a mammal. Applicants contend that Carr fails to anticipate claim 16.

The Office Action also takes a position that Carr anticipates claim 16 because the administered MTBE solvate or cyclohexane solvate would be expected to dissolve in the human body resulting in fexofenadine HCl in the human body. Thus, the Office Action asserts that the method of claim 16 would result in administering fexofenadine HCl as the active ingredient, which is the same active ingredient administered in the method of Carr. Applicants contend that even though the Form IX-MTBE solvate or Form IX-cyclohexane solvate would yield fexofenadine in the body after administration, Carr does not anticipate claim 16 because Carr does not teach the administration of fexofenadine HCl Form IX-MTBE solvate or Form IX-cyclohexane solvate.

Withdrawal of the anticipatory rejection of claim 16 over Carr is requested.

#### **Claim Rejections -- 35 U.S.C. § 103(a)**

Applicants respectfully traverse the rejections of claims 1-3 and 14-16 as obvious under 35 U.S.C. § 103(a) over Ortyl '872 in view of Evans, US Pharmacopoeia and Brittain, supplemented with Gottlieb.

As discussed above, Ortyl '872 differs from claims 1-3 and 14-16 at least in not disclosing the fexofenadine hydrochloride crystalline forms with the characteristic PXRD peaks recited in claim 1 or substantially as depicted in Fig. 6. The four crystalline forms

of fexofenadine hydrochloride disclosed by Ortyl '872 are different from the fexofenadine hydrochloride solvate according to claims 1-3 and the Form IX-MTBE solvate or Form IX-cyclohexane solvate in the pharmaceutical composition of claim 14, the unit dosage of claim 15 and the pharmaceutical composition administered in the method of claim 16.

The Office Action relies on Evans for the teaching that crystalline organic materials having suitable interstitial space would entrap solvents. The Office Action asserts that US Pharmacopoeia discloses that solvates of a known compound may display different XRD but whether they are true polymorphs must be evaluated carefully. The Office Action indicates that Brittain discloses that many organic crystalline compounds can form crystalline solvates, which can be obtained using ordinary laboratory solvents. The Office Action asserts that Gottlieb teaches that cyclohexane and MTBE are ordinary laboratory solvents.

The Office Action alleges that the instant claims would have been obvious over the cited prior art because a person having ordinary skill in the art would be motivated to prepare crystalline fexofenadine HCl by picking and choosing alternative ordinary laboratory solvents instead of ethyl acetate used in the prior art with the expectation to obtain crystalline solvates of the known crystalline fexofenadine HCl with small differences in X-ray diffraction patterns. Applicants disagree. Evans, US Pharmacopoeia and Brittain supplemented with Gottlieb fail to cure the deficiencies of Ortyl '872 because Evans, US Pharmacopoeia, Brittain and Gottlieb are silent on fexofenadine hydrochloride, let alone crystalline forms of fexofenadine HCl, or solvates of crystalline forms of fexofenadine HCl. Evans, US Pharmacopoeia and Brittain supplemented with Gottlieb do not provide any teaching or suggestion to modify the disclosures of Ortyl '872 to arrive at the claimed invention. A person of ordinary skill in the art would not be motivated to convert the crystalline fexofenadine HCl forms disclosed by Ortyl '872 into a solvate form of an organic solvent because Ortyl '872 merely discloses crystalline anhydrous fexofenadine HCl or crystalline hydrated fexofenadine HCl. Ortyl '872 does not disclose any organic solvent solvate of crystalline anhydrous fexofenadine HCl. Even if the person of ordinary skill in the art were to modify the prior art process by replacing ethyl acetate with another ordinary laboratory solvent, there are too many

ordinary laboratory solvents to choose from, with no guidance toward picking MTBE or cyclohexane. In addition, the person of ordinary skill in the art would not be motivated to replace ethyl acetate with MTBE or cyclohexane because ethyl acetate is more polar than MTBE and cyclohexane. There would have been no reasonable expectation of success of using MTBE or cyclohexane instead of ethyl acetate. Due to at least the above reasons, claims 1-3 and 14-16 would not have been obvious over the prior art relied upon by the Office Action.

In the event that the filing of this paper is deemed not timely, applicants petition for an appropriate extension of time. The petition fee and any other fee that may be required in relation to this paper can be charged to Deposit Account No. 11-0600.

Respectfully Submitted,  
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